Drug Eluting Stents for Symptomatic Intracranial and Vertebral Artery Stenosis

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Summary

The use of bare metal stents (BMS) to prevent recurrent stroke due to stenosis of the cerebral vasculature is associated with high rates of restenosis. Drug-eluting stents (DES) may decrease this risk. We evaluated the performance of DES in a cohort of patients treated at our institution.

Consecutive patients treated with DES were identified by a case log and billing records; data regarding procedural details, clinical outcome and angiographic follow-up was obtained by retrospective chart review.

Twenty-six patients (27 vessels; 14 vertebral origin (VO); 13 intracranial) were treated. Stenosis was reduced from mean 81% to 8% at the VO and 80% to 2% intracranially. No strokes occurred in the first 24 hours after stenting or at any time point in the VO group during a mean follow-up period of nine months. Among patients with intracranial stents, stroke with permanent disability occurred within 30 days in 1/12 (8%) and after 30 days in 1/11 (9%) with clinical follow-up (mean follow-up, 14 months). Follow-up catheter angiography was obtained in 14/14 (100%) in the VO group at mean eight months and in 8/11 surviving patients (73%) at a mean of ten months after stenting in the intracranial group. The restenosis rate was 21% at the VO (3/14) and 38% (3/8) for intracranial stents.

Restenosis at the VO was less frequent than might have been expected from reports utilizing BMS, however, overall restenosis rates appeared higher than previously reported for patients with intracranial DES and comparable with restenosis rates for intracranial BMS.

Introduction

The one year risk of recurrent stroke due to intracranial stenosis among patients with recent stroke and high grade (≥70%) stenosis is 23% [1]. Patients presenting with TIA or stroke who are found to have severe extracranial carotid or vertebral artery stenosis also have a markedly increased risk of recurrent stroke as compared to those without arterial stenosis (OR 4. 7) [2] and the risk of recurrent stroke due to extracranial vertebral stenosis is roughly equivalent to that of carotid stenosis [3].

While stenting may decrease recurrent ischemic events [4], the utility of bare metal stents has been limited by restenosis rates of up to 36% at six months for intracranial vessels [4,5] and even higher rates at the vertebral origin (VO) [4,6-8]. Preliminary experience with drug-eluting stents (DES) in the cerebral circulation suggests a reduction in restenosis, though these reports have consisted of small series limited, in most cases, by incomplete angiographic follow-up [9-12]. We therefore reviewed the experience at our institution with DES.

Materials and Methods

Consecutive patients treated with DES for symptomatic intracranial or vertebral artery stenosis at a single university medical center between August 2004 and December 2007 were identified retrospectively by administrative billing records and a case log kept by one of the investigators. Clinical and angiographic data

were then obtained retrospectively by review of hospital and clinic charts as well as by direct review of radiologic imaging. This retrospective study was approved by the Institutional Review Board. Because of high rates of restenosis with bare metal stents placed at the VO observed in prior studies [4,6,7], DES were preferentially employed at this location.

All patients were evaluated by the stroke neurology team. Patients were considered for stenting at the VO if either: cerebral ischemia was presumed to result from atheroembolism from the VO or cerebral ischemia was presumed to result from hemodynamic insufficiency (posterior circulation TIA or stroke with high grade VO stenosis and contralateral atretic or occluded vertebral artery). Patients were considered for intracranial stenting if they presented with TIA or stroke referable to a high grade stenosis of a major intracranial artery.

All patients were co-managed by the stroke service. Medical management evolved over the course of the study as new data from several influential trials became available. With the publication of the SPARCL trial in 2006 [13], statin therapy was initiated in all ischemic stroke patients in the first 24 hours after diagnosis. Prior to this point, fasting cholesterols were obtained in all patients but statins were administered only to patients with documented hypercholesterolemia. In the period after presentation and before stenting, permissive hypertension (systolic blood pressure < 200 mmHg) was commonly allowed in the first week after stroke. In TIA patients and in stroke patients after the initial period of permissive hypertension, relatively high blood pressures were tolerated (systolic blood pressure <180) until the publication in 2007 of the substudy from the WASID trial suggesting increased stroke risk in patients with elevated systolic blood pressure [14]. Subsequently, prior to stenting, a target blood pressure of <=140 was generally chosen. Throughout the study period, after stenting, blood pressure was treated aggressively according to JNC 7 guidelines [15].

Prior to the procedure, patients received either 5 days of clopidogrel 75 mg and aspirin 325 mg or a loading dose of clopidogrel 600 mg and aspirin 325 mg administered at least four hours prior to the procedure. Afterward, patients received six months of clopidogrel 75 mg/d and aspirin 325 mg/d followed by aspirin monotherapy continued indefinitely.

A 5F diagnostic catheter was navigated proximal to the lesion and diagnostic angiography was performed. Heparin bolus (5000U) was then given and heparin was subsequently titrated to ACT≥250 during the case (it was not continued in the peri-operative period). Next, for intracranial procedures, the diagnostic catheter was exchanged for a 6F sheath with a coaxial 6.5F JB-1 slip catheter over a 300 cm exchange wire. For the vertebral origin, a 6F shuttle was generally used but a 7F shuttle and 7F Brite Tip guide catheter (Cordis, Bridgewater, NJ, USA) coaxial support system was used when substantial tortuosity was present. The slip catheter and exchange wire were then removed and a 0.014 inch Synchro II microguidewire (Boston Scientific, Natick, MA, USA) was placed across the lesion, allowing for the passage of an SL-10 microcatheter (Boston Scientific, Natick, MA, USA). A 300 cm Transcend 0.014 inch exchange wire (Boston Scientific, Natick, MA, USA) was then introduced and the microcatheter was removed. In most cases, pre-stent angioplasty was performed with a Gateway balloon (Boston Scientific, Natick, MA, USA) with inflation times of five to ten seconds in order to facilitate the passage of the stent across the lesion. Afterward, Taxus (tacrolimus-eluting, Boston Scientific, Natick, MA, USA) or Cypher (sirolimus-eluting, Cordis Corp, Bridgewater, NJ, USA) balloon-mounted stents were placed. Stents were chosen to completely cover the stenotic portion with at least 2 mm of overlap with the non-stenotic portion and to match the normal diameter of the artery. Balloons were inflated slowly over five to ten seconds.

Control angiography was performed immediately afterward with determination of the degree of residual stenosis. Follow-up clinical and angiographic evaluation was scheduled at six months for all patients and on an as-needed basis thereafter. Restenosis was defined as narrowing ≥ 50% of the vessel lumen.

Results

Twenty-six patients were treated with 27 drug-eluting stents (14 VO; 13 intracranial; Table 1). All patients presented with TIA or stroke. Among patients undergoing stenting at the VO, the average age was 72, a history of stroke prior to stenting was present in 43%, and the most recent ischemic symptoms occurred within 17 days in 62%. Among patients undergoing intracranial stenting, the mean age

Table 1 **Baseline clinical features.**

	VO	Intracranial
Demographics		
Number of patients	14	12
Number of stents	14	13
Age–mean ± SD	72	66
Male–*n* (%)	11 (79%)	7 (58%)
Indication		
Stroke (with or without TIA)–*n* (%)	6 (43%)	10 (83%)
TIA only–*n* (%)	8 (57%)	2 (17%)
Entry event		
≤ 17d–*n* (%)	8 (62%)	9 (75%)
Comorbidities		
Hypertension	13 (93%)	12 (100%)
Coronary artery disease	5 (36%)	5 (42%)
Diabetes Mellitus	3 (21%)	4 (33%)
Hypercholesterolemia	7 (50%)	7 (58%)
Smoking	3 (21%)	4 (33%)
Medical treatment (prior to last ischemic event)		
Antiplatelet–*n* (%)	11 (79%)	10 (83%)
Anticoagulation–*n* (%)	4 (29%)	5 (42%)
Statin–*n* (%)	8 (57%)	6 (50%)
Antihypertensives–*n* (%)	12 (86%)	10 (83%)

was 66 years, a history of stroke prior to stenting was present in 83%, and the most recent ischemic event occurred within 17 days in 75%. Risk factors for atherosclerotic disease were present in nearly all patients in both groups.

Procedural details and 30 day clinical follow-up were available for all 26 patients. DES were successfully deployed in 100% of vessels attempted, with a reduction in stenosis in the VO and intracranial groups before and after stenting from 81% to 8% and 80% to 2% respectively (Table 2). The mean and median dimensions of stents placed at the VO were 3.1×12.1 and 3.5×12 respectively. Intracranially, the mean was 3.0×13.2 and median 3.0×12. No major and 2 minor complications (groin hematomas) occurred within 24 hours of the procedure. Three ischemic events, all in the group undergoing intracranial stenting, occurred at between 24 hours and 30 days after stenting – one TIA (8%) and two strokes (16%; one with persistent weakness of the left upper extremity and one with complete resolution within 48 hours of onset). All of these perioperative ischemic events occurred within territory of the treated artery.

Two patients died within three months of intervention (breast cancer, COPD), both in the intracranial stenting cohort. Follow-up angiography was completed in all patients who underwent stenting at the VO and in 8/11 (73%) of the surviving patients in whom intracranial stenting was performed (Table 2). The overall restenosis rate was 27%: 21% at the VO and 38% in intracranial locations. All stents were stable in comparison to the initial angiogram with complete wall apposition. Six patients underwent catheter angiography at a mean of 7.3 months after the six-month follow-up angiogram. None had more than 10% progression of restenosis in comparison to their initial angiogram. Restenosis was significantly associated with diabetes (OR 6.1, p=0.03) and coronary artery disease (CAD, OR 4.4, p=0.05). Of the patients with restenosis, 33% had a stroke or TIA.

Clinical follow-up was available for 100% of surviving patients, with last follow-up at a mean ± SD of 11.3 ± 8 months after treatment. No strokes were observed in patients with stents at the VO. The risk of stroke at >30 days among patients treated with intracranial stents was 18% (one major stroke within the territory of a restenosed vessel and one minor stroke, with full recovery, due to intracranial stenosis of vessels not associated with the stent). The risk of stroke with permanent neurologic deficits at any point after stenting among patients surviving more than three months was 0% in the VO group and 18% in the intracranial stenting group. No clinical signs of central nervous sys-

Table 2 **Perioperative results, follow-up angiography, and clinical follow-up.**

	VO	Intracranial
Perioperative results		
Vessel treated Vertebral origin–*n* Vertebral intracranial–*n* (% of intracranial) Basilar–*n* (% of intracranial) Internal carotid–*n* (% of intracranial) Middle cerebral–*n* (% of intracranial)	14	 3 (23%) 4 (31%) 5 (38%) 1 (8%)
Degree of stenosis–mean ± SD Before After	 81%±6% 8%±11%	 80%±10% 2%±4%
Stent used Taxus Cypher Stent dimensions, mean (mm) Stent dimensions, median (mm)	 10 4 3.1×12.1 3.5×12	 12 1 3.0×13.2 3×12
Major perioperative complications (<24 h)	0 (0%)	0 (0%)
TIA or ischemic stroke at ≤30 days–*n* (%) TIA Minor stroke (complete recovery) Stroke with persistent neurologic deficit Stroke, total	 0 (0%) 0 (0%) 0 (0%) 0 (0%)	 1 (8%) 1 (8%) 1 (8%) 2 (16%)
Follow-up catheter angiography		
Angiogram completed–*n* (% surviving >3 mths)	14 (100%)	8 (73%)
Time to last angiogram–mean±SD, mths	8±4	10±8
Degree of restenosis–mean±SD	32%±37%	37%±45%
Restenosis ≥ 50%–*n* (%)	3 (21%)	3 (38%)
Symptomatic restenosis–*n* (%) (relative to total number of stents placed)	1 (7%)	1 (13%)
Symptomatic restenosis–*n* (%) (relative to total number of vessels restenosed)	1 (33%)	1 (33%)
Clinical follow-up		
Clinical follow-up available–*n* (% surviving > 3 mths)	14 (100%)	11 (100%)
Last follow-up–mean ± SD, mths	9±6	14±9
TIA or stroke at >30days–*n* (%) TIA Minor stroke (complete recovery) Stroke with persistent neurologic deficit Stroke, total	 2 (14%) 0 (0%)	 0 (0%) 1 (9%) 1 (9%) 2 (18%)
TIA or stroke at any time point TIA Stroke Stroke with persistent neurologic deficit	 2 (14%) 0 (0%) 0 (0%)	 2 (18%) 4 (33%) 2 (18%)

Table 3 **Studies reporting more than 10 patients utilizing drug-eluting stents for intracranial stenosis.**

Ref	N	Clinical follow-up (mths)	Rate of clinical follow-up (%)	Angiographic follow-up (mths)	Rate of angiographic follow-up	Stroke risk	Restenosis rate	Extracranial vertebral artery (% of treated cases)
(10)	18	14	100%	6	39%	0.14	0.14	0
(11)	13	10	92%	5.4	69%	0.15	0	0
(9)	62*	n/a	n/a	4	81%**	n/a	0.06	50%
(12)	10	12	100%	12	100%	0	0	100%
Weighted Average	**103**	**12**	**39%**	**5**	**74%**	**11%**	**5%**	**40%**

** Includes 31 stents placed in extracranial vertebral artery*
*** Catheter angiography in 41; CT angiography in 7.*

tem toxicity arising from the drugs eluted by the stents were observed.

Discussion

We treated 26 patients (27 vessels) with drug-eluting stents. Technical success was 100% and there were no instances of cerebral ischemia intraprocedurally or within the first 24 hours after stenting. Deliverability of balloon-mounted stents to the intracranial circulation has been an issue in the past. The high degree of technical success and the absence of immediate periprocedural complications likely reflects improvements in stent trackability, access devices and wire technologies. Within the first 30 days, no strokes occurred in the patients undergoing stenting at the VO, whereas 2/12 (16%) of the patients with intracranial stents had strokes within the first 30 days after the procedure (one with complete recovery and one with persistent neurologic deficit). Among patients surviving three months or more, the risk of stroke with permanent disability at any point (peri-procedural or post-procedural) was 0% in the VO group and 22% in the intracranial group. The risk of restenosis was 21% at the VO and 38% intracranially.

In comparison to bare metal stents, the 21% risk of restenosis in our cohort appeared to be somewhat reduced at the VO in comparison to that expected from bare metal stents but somewhat higher than many reports of DES in this location. At the VO, restenosis with bare metal stents occurs in about 40% of patients [7]. A recent review identified 104 cases of DES placed at the VO, of which 54 (52%) underwent follow-up angiography. Restenosis was found in 6/54 (11%) [7]. A large single center case series was published after the review. In this series of 47 patients, of whom 80% underwent follow-up angiography, an in-stent restenosis rate of only 5.3% was found [8].

The major intracranial bare metal stent registries have reported restenosis rates of 25% at 4.8 months [16] and 36% at six months [4]. By contrast, several investigations have revealed substantially lower restenosis rates with drug-eluting stent placement–6% at four months [9], none at five months [11], 14% at six months [10], and none at 12 months [12] placed in the intracranial circulation (Table 3). What accounts for the 38% rate of restenosis in our cohort?

One possibility is simply that angiographic follow-up in our study was more complete and occurred at a longer time frame after drug-eluting stent placement than in prior reports. Taken together, these reports include 103 vessels, with mean rates of clinical and angiographic follow-up of only 39% and 74% respectively and mean time to angiography of only five months. Excluding follow-up with CTA and considering only those patients followed by catheter angiography, the rate of follow-up in these studies was 65%. We obtained follow-up angiography in 64% of patients at mean of ten months after stent placement. As may be true in the coronary circulation [17,18], drug-eluting stents in cerebral vessels may prevent early restenosis but carry a risk of delayed restenosis. It is also possible that the duration of dual antiplatelet therapy may have played a role. During the study period, aspirin was continued indefinitely but clopidogrel for only six months (we have since extended dual antiplatelet therapy to one year).

The vertebral origin differs from the intracranial circulation embryologically and anatomically and these differences may explain the lower rates of restenosis seen at the VO compared with intracranial locations. Whereas the vertebral artery origins typically are derived from the seventh dorsal intersegmental arteries [19], the intracranial vasculature is derived from the third aortic arches, the dorsal aortae, and the dorsal longitudinal neural arteries [20]. In addition, some evidence from the coronary literature suggests that DES have substantially lower rates of restenosis as compared to BMS when used to treat ostial lesions in particular [21].

The risk of stroke in the intracranial stent cohort was relatively high: 33% had a stroke at some point during follow-up and 18% of patients had a stroke leading to a permanent neurological deficit. While the number of patients enrolled in our study was low, there does not appear to be a substantial risk reduction compared to the 23% risk of stroke in the first year observed in high risk patients in the Warfarin versus Aspirin for Symptomatic Intracranial Disease (WASID) trial [1]. Ultimately, randomized trials such as the Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) and Vitesse Intracranial Stent Study for Ischemic Therapy (VISSIT) will be necessary to provide answers about whether the currently available intracranial stents are efficacious in preventing recurrent stroke due to intracranial stenosis [22].

Our study has several limitations. Even though follow-up data were available for a substantial majority of patients, 12% did not have a follow-up angiogram and 4% did not have clinical follow-up. Second, although patients were identified prospectively, data acquisition was retrospective.

Conclusion

In summary, we retrospectively reviewed the performance of drug eluting stents in a consecutive series of 26 patients (27 vessels) in the cerebral vasculature. The risk of restenosis appears to be reduced by the use of DES at the VO. Restenosis at the VO occurred in 21% of our patients, whereas restenosis rates of approximately 40% are expected with bare metal stents. In our series, DES in the intracranial circulation did not appear to affect the risk of restenosis. Restenosis occurred in 38% of patients in our cohort, a rate comparable to intracranial bare metal stents and higher than that observed in previous studies of DES in the intracranial circulation. The higher rate of restenosis in our cohort may reflect longer angiographic follow-up times than most prior studies. These results suggest that DES may reduce restenosis rates when used at the VO not when used intracranially.

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